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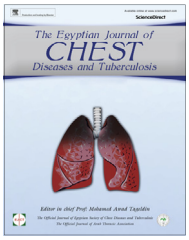

ORIGINAL ARTICLE

# Difficult to treatment asthma, is it really asthma? Is it really difficult?

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**KEYWORDS**

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**Abstract** With the judicious use of inhaled corticosteroids (ICS) and $B_2$ agonists most patients with asthma are easily controlled and managed. However, approximately 5–10% of asthmatics did not respond to standard therapy and are classified as "difficult to treat asthma, DTA". Many factors can contribute to poor response to conventional therapy. For these patients, a systematic approach is needed to identify false (non-genuine) DTA from true (genuine) intractable DTA. It is essential to sort through and address the above issues before reverting to other therapy.

*Objectives:* The aim of the present study is to evaluate a systematic approach to indentify the patients of false (non-genuine) to true (genuine) DTA and to recognize the underlying different precipitating factors.

*Conclusion:* In apparently DTA there is a high prevalence of false (non-genuine) cases. Identification and management can be achieved by detailed systematic assessment.


## Introduction

Asthma is a major public health problem. Its worldwide prevalence is estimated at 10% and is still increasing [1–4].

Small percentage of asthmatic patients (5–10%) are not well controlled despite the use of high dose inhaled corticosteroids (ICS), long acting bronchodilators (LABA), plus add on treatment. These patients are attributed to have Difficult-to-treat asthma (DTA) [5]. DTA carries several names; each one points to an aspect of the disease. "Chronic severe asthma" [5], "steroid-dependent asthma" [6], "steroid-resistant asthma" [7], "difficult-to-control asthma" [5], "resistant asthma" [6] and "refractory asthma" [7] are some of these terminologies. Although these patients make small percentage of all asthmatics, they account for 50% of the total cost of asthma therapy [8]. Mortality, morbidity, steroid side effects and health costs are disproportionately high in these patients, and they are at greater risk of acute severe, near fatal, and fatal exacerbations [7].

Many factors can contribute to poor response to conventional therapy. For these patients, a systematic approach is needed to identify false (non-genuine) from true genuine intractable DTA [9].

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False (non-genuine causes) DTA can be divided into three categories: (1) misdiagnosis where the problem is not asthma from start [10] (e.g. psychiatric disorders, chronic obstructive pulmonary disease (COPD), congestive heart failure (CHF), interstitial lung disease (ILD), upper airway disease (UAWD), bronchiolitis obliterans (BO), and pulmonary infiltrates with esinophilia (PIE)), (2) presence of confounding factors (e.g. poor inhaler technique, persistent exposure to provoking factors, non-adherence to treatment and drug intake e.g. NSAIDs or B blockers) and (3) comorbidities that worsen asthma and making it difficult to treat (e.g. chronic rhinosinus disease, gastroesophageal reflux disease (GERD), obstructive sleep apnea syndrome (OSA), psychiatric disorders, vocal cord dysfunction syndrome (VCD) and hypothyroidism) [11]. It is essential to sort through and address the above issues before reverting to other therapy [12–14].

### Aim of the present study

The aim of the present study is to evaluate a systematic approach to identify false (non-genuine) to true (genuine) DTA patients and to recognize the prevalence of the underlying different precipitating factors.

### Patients and methods

The present cross-sectional study was performed in the outpatient asthma clinic, Fayoum University Hospital, Department of Chest Diseases, Faculty of Medicine, Fayoum University. In this study, 200 patients provisionally diagnosed as apparently DTA aged 9–69 yrs, were consecutively recruited from 7 different general hospitals, many primary health care units, many private clinics in the region of Fayoum Governorate. The patients were all treated with $\geqslant 2000\ \mu g\ day^{-1}$ of beclomethazone dipropionate (BDP) or its equivalents with long-acting bronchodilators. DTA was defined on the basis of clinical assessment, treatment requirements and fulfill the diagnostic criteria of DTA according to the American Thoracic Society [7,15]. Patients were all nonsmokers or light smokers (smoking history < 10 pack-yrs) [14].

At the first visit, patients' characteristics were documented according to a structured questionnaire. Full clinical history was recorded for all subjects and a thorough physical examination was performed. All patients were submitted for routine laboratory profile, CXR, pulse oximetry for arterial oxygen saturation and forced spirometry with reversibility testing. Diagnosis of asthma was defined on the basis of typical symptoms together with current or recently documented reversibility in forced expiratory volume in 1st second ($FEV_1$) of $>15\%$. $FEV_1$ was assessed before and 30 min after the nebulization by 5 mg salbutaomol and 500 μg ipratropium and expressed as percentage of predicted value [16]. Reversibility in $FEV_1$ was defined as follows [16]: $(FEV_{1\ POST} - FEV_{1\ PRE}/FEV_{1\ PRE})$. In non-asthmatic patients, we search for another disease causing these misdiagnoses. General Health Questionnaire (GHQ) was used to evaluate each patient's psychological functioning. This is the most widely used scoring test used to detect psychiatric disorders in medical practice. It measures the presence of non-psychotic psychiatric disturbances specifically anxiety and depression disorders. The short GHQ-12 version (score range 0–12) was used, with a score $\geqslant 6$ indicating possible psychiatric cases [17]. COPD was diagnosed according to GINA criteria [1]. CHF was diagnosed according to clinical, radiological and echocardiographic criteria. ILD was diagnosed according to clinical, functional and HRCT chest criteria. Bronchiectasis was diagnosed according to clinical and HRCT chest criteria. UAWD was diagnosed according to clinical, flow-volume loop, radiological, and fiberoptic laryngoscopic criteria. BO was diagnosed according to clinical, functional, and HRCT chest criteria. PIE was diagnosed according to clinical, laboratory, radiological and bronchoalveolar lavage findings [6,7].

At the second visit, confounding factors were reviewed (either poor inhaler technique, persistent exposure to provoking factors, poor adherence or drug intake e.g. NSAIDs, B blockers). Inhaler technique was reviewed and patients were provided with the device they found most suitable and could use properly (including the provision of combination inhalers). Detailed history was taken to detect any persistent indoor or outdoor exposure to provoking factors (either non-specific or specific allergens). If an external provoking factor was identified for example, occupational exposure, domestic allergen or particular food-subjects were encouraged to take steps to exclude the provoking factor.

At the third visit precipitating comorbidities that worsen asthma and making it difficult to treat were reviewed. Severe rhinosinus disease was considered to be present if there are symptoms of itching of nose, sneeze, rhinorrhoea, nasal obstruction or post-nasal discharge with a successful trail of topical steroids, oral antihistaminics and alkaline nasal wash. If there is no improvement the patient was shifted to ENT clinic. GERD was considered to be present if there is severe reflux symptoms improved with a successful trial of proton-pump inhibitors and GIT prokinetics. OSA was considered a potential contributing factor if the clinical criteria were met by overnight pulse oximetry revealed AHI $>5$/h [10]. General Health Questionnaire (GHQ) was used to evaluate each patient's psychological functioning as previously mentioned. Vocal cord dysfunction syndrome was considered to be present if there are clinical symptoms of noisy breathing and dyspnea, laryngoscopic evidence of vocal cord adduction with or without flattening of the inspiratory limb of flow-volume loop [18]. Hyperthyroidism was present with an elevated level of free thyroxin ($>24\ pmol\ L^{-1}$) [17].

All patients were followed up for a minimum period of 3 months after protocol assessment. If asthma symptoms were controlled, subjects are classified as having false (non-genuine) DTA and were discharged. Co-existent diagnoses were managed using standard treatments.

### Results

Prevalence of potential contributing factors in the 200 patients with DTA who participated in the study and patients' characteristics are given in Tables 1–4 and Figs. 1, 2.

### Discussion

The results of the present study show that 90% of the apparently diagnosed DTA may not so be. False (non-genuine) DTA in these patients were strongly associated with

**Table 1** Patient characteristics of the study population.

| | |
|---|---|
| Subjects *n* | 200 |
| Age yrs | 41.6 ± 32.6 |
| Female % | 70% |
| Age at onset asthma yrs | 8.9 (0.7–60) |
| Asthma duration yrs | 18.0 (3–61) |
| Dose of ICS[a] | 1500 (1500–4000) |
| Maintenance oral steroids % | 10 |
| Smoking history pack.yrs$^{-1}$ | 3 (0–10) |

[a] Beclomethasone dipropionate or its equivalent in μg/day.

**Table 2** Percentage of false (non-genuine) to true (genuine) DTA patients.

| | |
|---|---|
| Subjects *n* | 200 |
| False (non-genuine) DTA | 180 (90%) |
| True (genuine) DTA | 20 (10%) |

**Table 3** Potential prognostic factors at presentation for having true (genuine) DTA after variables were dichotomized using logistic regression analysis.

| | |
|---|---|
| ICS > 2000 μg at referral | 7.4 (3.5–21.7) |
| Previous pulmonologist attendance | 3.9 (2.7–13.6) |
| Pre-bronchodilator $FEV_1$ < 70% | 5.1 (3.2–14.7) |

**Table 4** Prevalence of underlying different factors in false (non-genuine) DTA.

| | |
|---|---|
| Subjects *n* | 180 |
| Misdiagnosis | 60/180 (33%) |
| Psychiatric disorders | 18/60 (30%) |
| COPD | 15/60 (25%) |
| CHF | 9/60 (15%) |
| ILD | 7/60 (11.6%) |
| Bronchiectasis | 5/60 (8.3%) |
| UAWD | 3/60 (5%) |
| BO | 2/60 (3.3%) |
| PIE | 1/60 (1.6%) |
| Confounding factors | 40/180 (22.2%) |
| Poor inhaler technique | 20/40 (50%) |
| Persistent exposure | 20 (50%) |
| Poor adherence | 13/40 (32.5%) |
| Drug intake | 9/40 (15%) |
| Comorbidities | 80/180 (44.4%) |
| Severe rhinosinus disease | 65/80 (81%) |
| GERD | 56/80 (70%) |
| OSA | 25/80 (31%) |
| Psychiatric disorders | 23/80 (28%) |
| VCD | 15/80 (18%) |
| Hyperthyroidism | 6/80 (7%) |

COPD = chronic obstructive pulmonary disease, CHF = congestive heart disease, ILD = interstitial lung disease, UAWD = upper airway disease, BO = bronchiolitis obliterans, PIE = pulmonary infiltrates with esinophilia, VCD = vocal cord dysfunction, GERD = gastroesophageal reflux disease, OSA = obstructive sleep apnea.

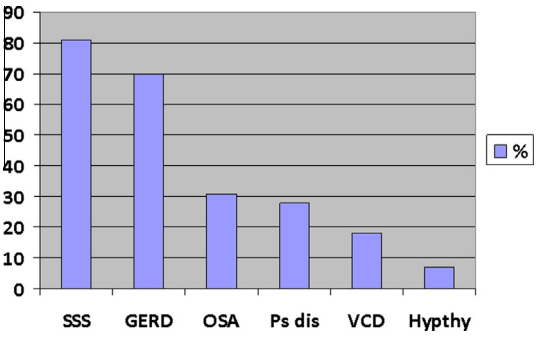


**Figure 1** Percentage of underlying comorbidities in the 80 patients who confirmed to be asthmatic and have another comorbidities which lead to their poor control ($n$ = 80). SSS = severe rhinosinus disease, GERD = gastroesophageal reflux disease, OSA = obstructive sleep apnea syndrome, Ps dis = psychiatric disease, VCD = vocal cord dysfunction syndrome, Hypthy = hyperthyroidism.

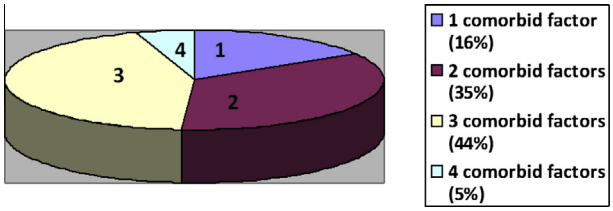


**Figure 2** Frequency distribution of comorbid factors (severe rhinosinus disease, GERD, OSA, psychiatric disorder, VCD, hyperthyroidism) which leads to poor control asthma. 1: one comorbid factor (occur in 16% of these group of patients); 2: two comorbid factors (35%); 3: three comorbid factors (44%); 4: four comorbid factors (5%).

misdiagnosis (33% of false DTA). These misdiagnosed diseases may be psychiatric disorders (30%), COPD (25%), CHF (15%), ILD (11.6%), bronchiectasis (8.3%), UAWD (5%), BO (3.3%) or PIE (1.6%). 22.2% of false (non-genuine) DTA are due to confounding factors (e.g. poor inhaler technique (50%), persistent exposure to specific or non-specific provoking factors (50%), poor adherence (32.5%) or drug intake (15%)). 44.4% of false (non-genuine) DTA are due to underlying unrecognized comorbidities. Severe rhinosinus disease occurs in 81% of patients in this group, while GERD occurs in 70%, OSA in 31%, psychiatric disorders in 28%, VCD in 18% and hyperthyroidism in 7%.

These findings emphasize the high prevalence of misdiagnosed asthma, presence of mostly unidentified confounding factors or existence of underlying unrecognized comorbidities. The findings of the present study suggest that the management of these factors may result in better control of the disease. A systematic evaluation protocol facilitates recognition and management of these factors and allows identification of the small sector – but troublesome – of these patients with true (genuine) DTA. Clinical improvement can be anticipated if patients with poorly controlled or DTA are submitted to a systematic evaluation protocol [19–20].

One previous systematic evaluation protocol for patients with DTA has been published [20]. This protocol evaluated 42 patients over an 8 yr period from 1982 to 1990 and concluded that, after working through the protocol, 74% were

no longer difficult to control which suggests that protocol guided care improves outcome both in terms of lung function and patients symptoms.

The present study reveals that patients with true (genuine) DTA tend to have both lower initial $FEV_1$% and lower best $FEV_1$% which are consistent with a greater degree of fixed airflow obstruction and airways remodeling. These fixed airflow obstruction and airway remodeling does not relate to the presence of previous or current smoking. This is consistent with previous studies showing significantly reduced lung function in subjects with severe asthma [21,22].

As our study was cross sectional, it is impossible to determine whether worse lung function causes true (genuine) DTA or vice versa. Given the prolonged period of instability and the fact that there was no difference in the duration of asthma, these observations suggest that unstable disease (which could be due to uncontrolled or a particular type of therapy resistant inflammation) is associated with progressive remodeling and an accelerated decline in lung function.

As anticipated, identifying a diagnosis in addition to asthma which contributed to symptoms was associated with false (non-genuine) DTA. In addition, prior assessment by another respiratory specialist was associated with true (genuine) DTA, although this did not appear to be related to the identification of additional diagnoses.

The present study suspect three variables (inhaled steroid dose $\geqslant 2000$ μg, pre-bronchodilator $FEV_1$ of $< 70\%$ on this dose of inhaled steroid, and previous respiratory specialist referral) which reflect relative steroid resistance and chronic unstable disease. It is interesting that a prebronchodilator $FEV_1$ of $< 70\%$ at presentation despite high dose inhaled steroids and long acting $\beta_2$ agonist predicted resistance to treatment.

In the true (genuine) DTA group the prebronchodilator $FEV_1$% at presentation was significantly lower than the best pre-bronchodilator $FEV_1$% during follow up, suggesting that it is the inability to maintain lung function at a certain level despite intensive treatment rather than the degree of fixed airflow obstruction that defines therapy resistant disease.

## Conclusions

The present study evaluates a cohort of sequentially referred patients with apparently DTA. 90% of them have false (non-genuine) DTA due to misdiagnoses, presence of confounding factors or existence of underlying unrecognized comorbidities. These data support the use of a detailed and systematic evaluation of this population.

## Conflict of interest

None declared.

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